30. The method according to claim 25, wherein the NSAID is chemically modified by covalent attachment thereto of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

31. The method according to claim 30, wherein said sulfur-containing functional group is sulfonate, reverse sulfonate, sulfonamide, reverse sulfonamide, sulfone, sulfoxide, sulfinate, or reverse sulfinate.

32. The method according to claim 25, wherein the NSAID is acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenprofen calcium, flurobiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, or flosulide.

33. The method according to claim 32 wherein said NSAID is naproxen, aspirin, ibuprofen, flurbiprofen, indomethacin, ketoprofen, carprofen, or etodolac.

34. The method according to claim 25 wherein the NSAID is administered to a subject for the treatment of a pathological condition.

35. The method according to claim 34 wherein said pathological condition is inflammation.

36. The method according to claim 34 wherein the NSAID is administered to a subject for the treatment of anelgesia.

37. A method for alleviating the systemic toxicity of a non-steroidal anti-inflammatory drug (NSAID), said method comprising chemically modifying said NSAID prior to administration to a subject, wherein said NSAID is chemically modified so as to

a) reduce the maximum concentration (C_{max}) relative to the unmodified NSAID and

b) maintain a therapeutically effective concentration of said NSAID in plasma upon administration to said subject.

38. A method for reducing the maximum concentration in plasma achieved upon administration of a non-steroidal anti-inflammatory drug (NSAID), said method comprising modifying the NSAID by covalent attachment thereto of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

39. A method for the controlled release *in vivo* of a non-steroidal anti-inflammatory drug (NSAID), said method comprising chemically modifying the NSAID so as to reduce the maximum concentration (C_{max}) achieved in plasma upon administration to a subject.

40. The method according to claim 39, said chemical modification comprising the covalent attachment thereto of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

41. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject a therapeutically effective amount of a chemically modified non-steroidal anti-inflammatory drug (NSAID),

wherein the NSAID is effective for treatment of said condition, and wherein the modified NSAID has a reduced C_{max} value.

42. The method according to claim 41, wherein said pathological condition is septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease, diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation, burn, infection, hemodialysis, chronic fatigue syndrome, stroke, cancers, cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, headache, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors, malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease, drug-induced lung injury, myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, or coronary artery disease.

43. The method according to claim 42, wherein said pathological condition is arthritis.

44. The method according to claim 43, wherein said arthritis is rheumetoid arthritis or osteoarthritis.

45. The method according to claim 42, wherein said pathological condition is headache.

46. The method according to claim 45, wherein said headache is a migraine.

47. The method according to claim 42, wherein said pathological condition is pre-menstrual syndrome..

48. The method according to claim 42, wherein said pathological condition is pain.

49. The method according to claim 48, wherein said pain is chronic pain.

50. The method according to claim 48, wherein said pain is post-surgical pain.

51. In a method for the administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject for the treatment of a pathological condition, the improvement comprising modifying the NSAID so as to reduce the C_{max} value achieved upon administration to a subject.

52. A method for the preparation of a modified non-steroidal anti-inflammatory drug (NSAID) having reduced propensity to induce side effects, said method comprising modifying the NSAID so as to reduce the C_{max} value achieved upon administration to a subject.

53. In a method for the administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject for the treatment of a pathological condition, the improvement comprising directly or indirectly covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

54. The method of claim 53 wherein said pathological condition is septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers,

inflammatory bowel disease, diabetes, arthritis, asthma, Alzheimer's disease, Parkinson's disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation, burn, infection, hemodialysis, chronic fatigue syndrome, stroke, cancers, cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDS, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington's disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors, malaria, hematologic cancers, myelofibrosis, lung injury, graftversushost disease, head injury, CNS trauma, hepatitis, renal failure, liver disease, druginduced lung injury, myasthenia gravis (MG), ophthalmic diseases, postangioplasty, restenosis, angina, or coronary artery disease.

55. In the treatment of a subject suffering from a pathological condition by administration thereto of a non-steroidal anti-inflammatory drug (NSAID), the improvement comprising covalently attaching said NSAID to a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety prior to administration thereof to said subject.

56. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject an effective amount of a non-steroidal anti-inflammatory drug (NSAID),

wherein said NSAID is effective for treatment of said condition, and

wherein said NSAID has been modified by the direct or indirect covalent attachment thereto of a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety.

57. A method for the preparation of a protected form of a non-steroidal anti-inflammatory drug (NSAID), said method comprising directly or indirectly covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID.

58. A method according to claim 57 wherein said NSAID is acetaminophen, aspirin, ibuprofen, choline magnesium salicylate, choline salicylate, diclofenac, diflunisal, etodolac, fenprofen calcium, flurbiprofen, indomethacin, ketoprofen, carprofen, indoprofen, ketorolac tromethamine, magnesium salicylate, meclofenamate sodium, mefenamic acid, oxaprozin, piroxicam, sodium salicylate, sulindac, tolmetin, meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, or flosulide.

59. A method for reducing the side effects induced by administration of a non-steroidal anti-inflammatory drug (NSAID) to a subject, said method comprising directly or indirectly covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID prior to administration to said subject.

60. A method for enhancing the effectiveness of a non-steroidal anti-inflammatory drug (NSAID), said method comprising directly or indirectly covalently attaching a sulfur-containing functional group containing an optionally substituted hydrocarbyl moiety to said NSAID.

61. A method for the prevention or treatment of an inflammatory or infectious disease in a subject in need thereof, said method comprising administering to said subject an amount of the compound of claim 1 effective to alleviate said condition.

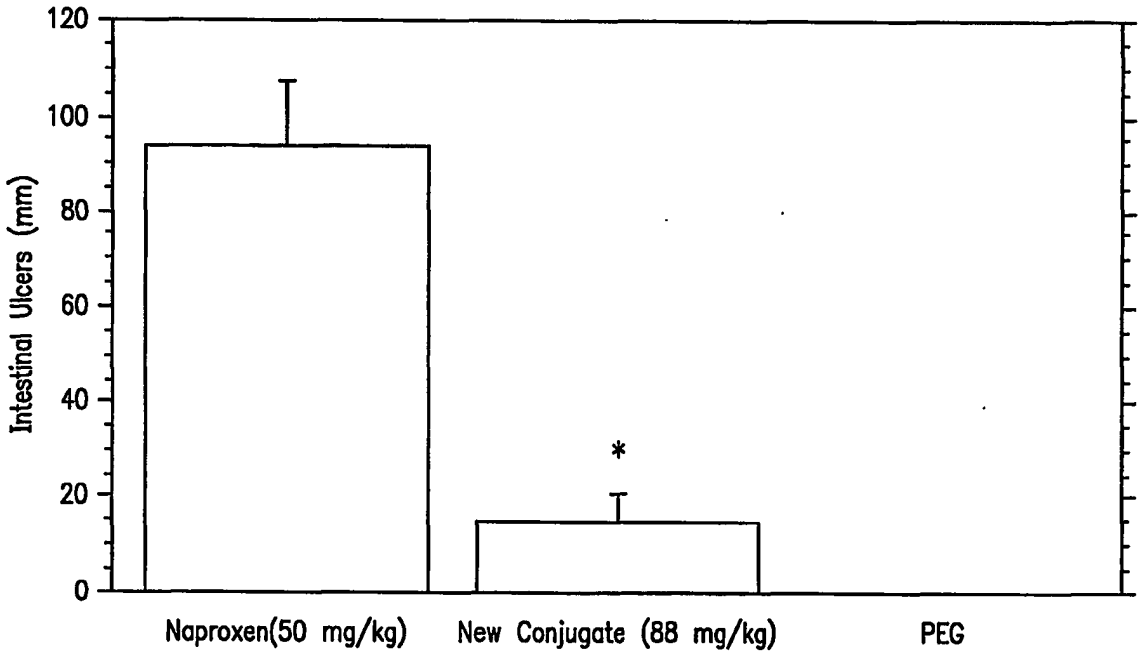

120
100
80
60
40
20
0
Intestinal Ulcers (mm)
*
Naproxen(50 mg/kg)
New Conjugate (88 mg/kg)
PEG

FIG. 1

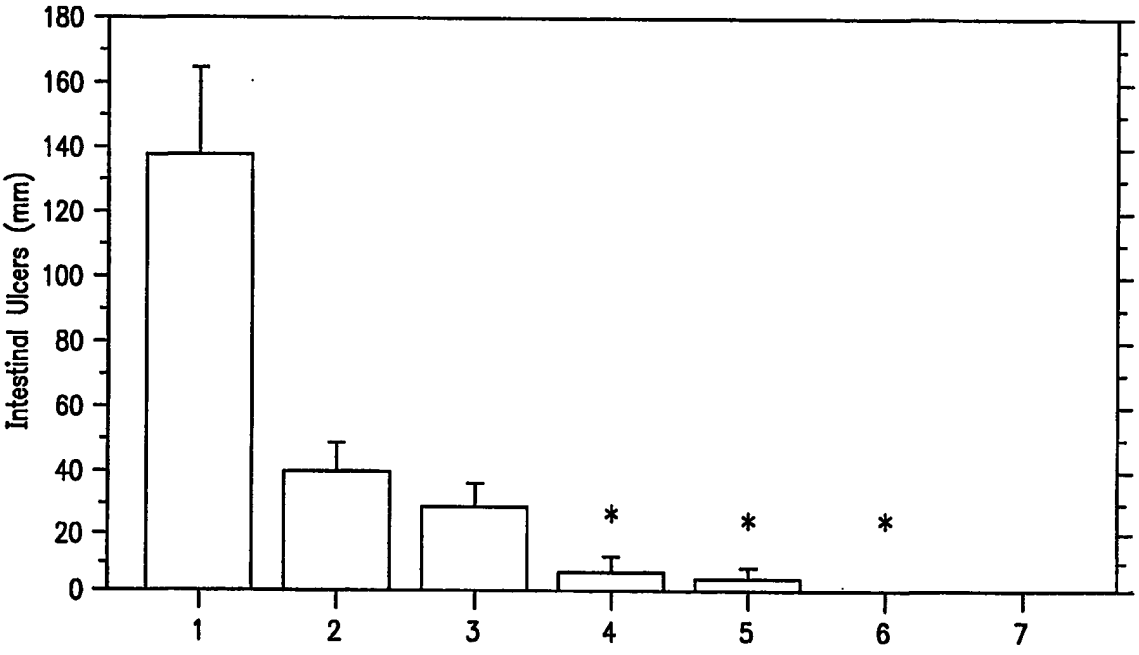


FIG. 2

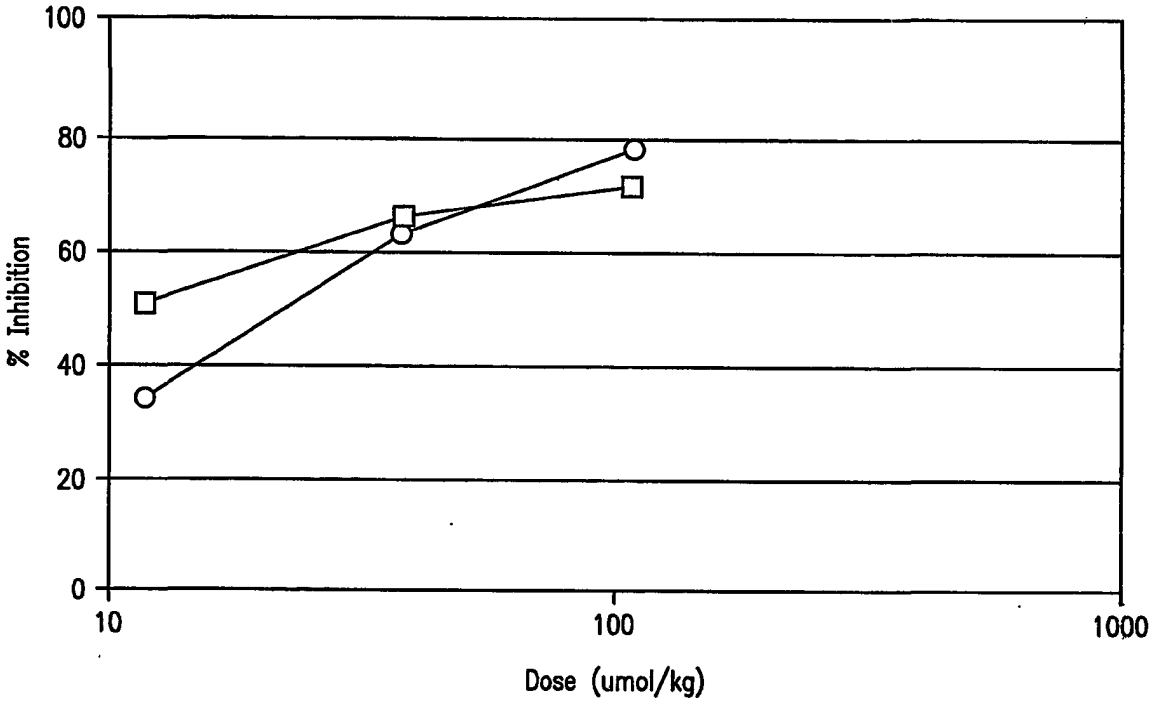


FIG. 3

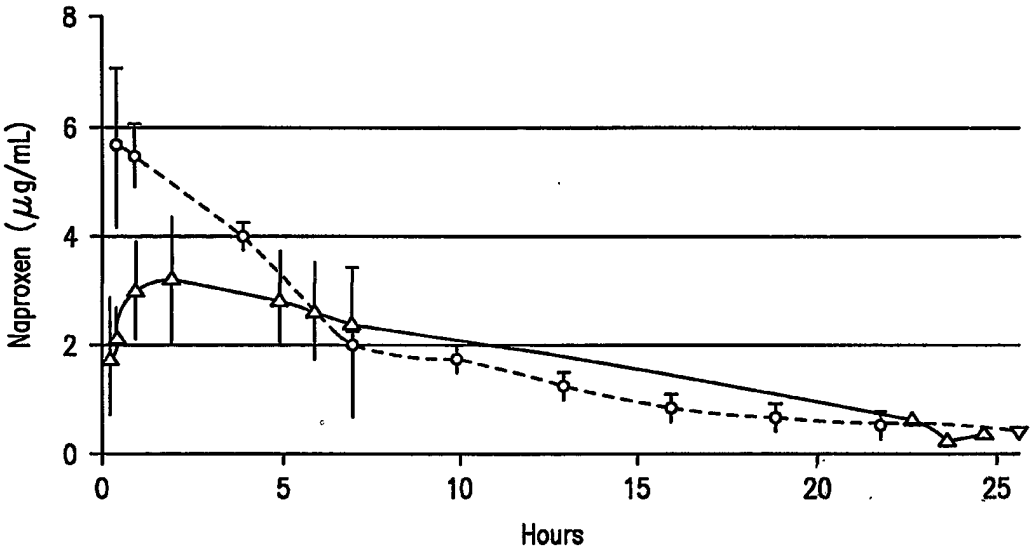


FIG. 4

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 440 098 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **91100947.0**

(51) Int. Cl.[5]: **C07C 327/32**, A61K 31/265

(22) Date of filing: **25.01.91**

(30) Priority: **29.01.90 IT 1918490**

(43) Date of publication of application:
07.08.91 Bulletin 91/32

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

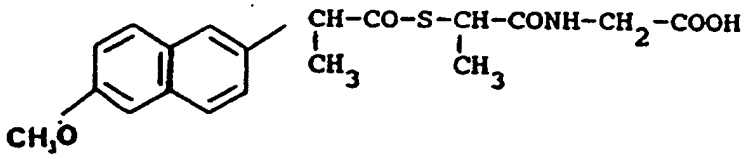
(71) Applicant: **FARMA RESA S.r.l.**
Via Como, 5
I-22063 Cantu' Como(IT)

(72) Inventor: **Reiner, Valentina**
Via Roma, 3
I-22010 Carate Urio(IT)
Inventor: **Sarda, Caterina**
Via Mentana, 23
I-22100 Como(IT)

(74) Representative: **Dragotti, Gianfranco et al**
SAIC BREVETTI s.r.l. Viale Bianca Maria, 15
I-20122 Milano(IT)

(54) Optically active derivative of d-2-(6-methoxy-2-naphthyl)-propionic acid and pharmaceutical compositions containing it.

(57) The S-[d-2-(6-methoxy-2-naphthyl)-propionyl]d-2-mercaptopropionamidoacetic acid having formula:



has improved therapeutical properties not only in comparison with the starting active principle, namely Naproxen, but also with respect to the corresponding racemic derivative, namely the (d,1) compound.

EP 0 440 098 A1

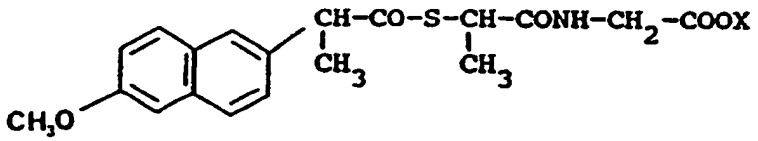
"OPTICALLY ACTIVE DERIVATIVE OF D-2-(6-METHOXY-2-NAPHTHYL)-PROPIONIC ACID AND PHARMACEUTICAL COMPOSITION CONTAINING IT"

The present invention relates to an optically active isomer of a derivative of d-2-(6-methoxy-2-naphthyl)-propionic acid, namely of the active principle known as Naproxen; the invention relates as well to pharmaceutical compositions containing the said derivative.

Naproxen is known since a number of years and is included among the substances having anti-inflammatory, analgesic and anti-pyretic activity: its main therapeutical use is the treatment of rheumatoid arthritis and of other degenerative forms having phlogistic features.

In turn alpha-mercaptopropionylglycine is a compound known as well, possessing it too anti-inflammatory activity besides the mucolytic activity.

The derivatives obtained by combining said two active principles are the object of the European Patent No. 124.925, which thus claims compounds having the following general formula:



wherein X is hydrogen or a radical selected among the radical of organic or inorganic, non toxic and pharmaceutically acceptable bases, radicals of basic aminoacids and radicals of basic antibiotics.

The characteristics and properties of the above mentioned compounds in the racemic form, namely the (d,1) form, are given in the specification and in the examples of this European Patent.

It has been now found and is the object of the present invention that the (d,d) diastereoisomer of the compound directly obtained from Naproxen and alpha-metilpropionylglicyine has surprisingly specific properties which are superior not only with respect with the starting active principle, namely Naproxen, but also with respect to the corresponding (d,1) racemic compound.

This greater activity over Naproxen is mainly seen in the lack of ulcerogenicity which is on the contrary the main drawback of Naproxen as regards the therapeutical use, whereas in comparison with the corresponding racemic compound the diastereoisomer of the present invention has greater analgesic activity.

Otherwise stated, the diastereoisomer of the present invention to the prevailing anti-inflammatory activity which is characteristics both of Naproxen and more remarkably of the derivatives being the subject of the European Patent 124.925, adds a specific analgesic activity which is definitely higher than that the of the corresponding racemic compound.

It is evident that the therapeutical use of these substances makes the symptomatic activity, namely the analgesic one, of the utmost importance.

As regards the preparation of the diastereoisomer of the present invention, reference is made to the specification and examples of European Patent 124.925, particularly examples 1a and 1b of this patent, which is herein included by reference.

Thus according to the process studied with respect to the present invention, the product of the reaction carried out between the acid chloride of d-2-(6-methoxy-2-naphthyl)-propionic acid and (2-mercapto-propionyl)-glycine in the presence of a base is poured in water, then an acidification is carried out with hydrochloric acid and the solid thus precipitated is filtered. For the separation of the desired (d,d) form the racemic one repeated fractionated crystallizations are carried out, using ethyl acetate as the crystallization solvent, until a product having constant melting point (180-1 °C) is obtained.

The obtained compound has been subjected to elemental analysis with the following results:
Calculated for $C_{19}H_{21}NO_5S$: %C 60.78; %H 5,63; %N 3,73; %S 8,54
Found: %C 61.02; %H 5.59; %N3,71; %S 8.63.

The (d,d) diastereoisomer of the invention is a crystalline solid having $[alpha]_D^{20}$ + 201.01 (C=1, methanol).

It is solubl in thanol, methanol and acetone, a little soluble in hot ethyl acetate and insoluble in water.

By carrying out the TLC analysis with chloroform: glacial acetic acid: water (85:15:0.5) as the eluant system, a value R_f = 0.75 is obtained whereas the (d,1) diastereoisomer has R_f =0.70.

The already mentioned properties of the diastereoisomer according to the invention have been confirmed by the pharmacologycal tests which are hereinafter shortly reported (the compound of the

invention is indicated in abbreviated form has d-d Nxtio whereas the other diastereoisomer is abbreviated as d-1 Nxtio).

As regards the anti-inflammatory activity the standard tests by means of carrageenan induced oedema and dextran induced oedema were performed whereas for the analgesic activity the writhing test and the Randall-Selitto test have been carried out.

1. Carrageenan induced oedema in the rat

Grups of 8 rats (Wistar-Charles River) have been orally administered with:
(i) vehicle alone (0.5% tragacanth);
(ii) d-d Nxtio at a constant volume of 24 ml/kg in the same vehicle;
(iii) d-1 Nxtio at constant volume of 25 ml/kg in the same vehicle.
The table 1 hereinafter reports the administration dosages.

TABLE 1

GROUP	TREATMENT VEHICLE	DOSE mg/kg p.o.
1	vehicle	---
2		6.25
3		12.5
4	d-d Nxtio	25.0
5		50.0
6		6.25
7		12.5
8	d-l Nxtio	25.0
9		50.0

Fourty five minutes later each rat received an injection of 0.1 ml of a 1% w/v suspension of carrageenan in sterile 0.9% saline, beneath the plantar aponeurosis of the left hind paw.

The volume of the paw was measured (in arbitrary units) before and 1.5, 3 and 6 hours after the irritant injection. The results are reported in the table 2, from which it can be observed not only that both diastereoisomers administered by oral route induce a significant inhibition of the carrageenan induced oedema, but also that d = 1 isomer is slightly less active than the d-d isomer.

TABLE 2

Effects of oral administration of d-d Nxtio and d-l Nxtio on a carrageenan-induced oedema in the rat

GROUP	TREATMENT	DOSE mg/Kg p.o.	MEAN INCREASE IN PAW VOLUME			% INHIBITION OF SWELLING		
			1.5	3	6	1.5	3	6
1	vehicle		7.9 +/- 0.58	12.1 +/- 0.52	13.4 +/- 0.76	-	-	-
2	d-d Nxtio	6.25	3.7 +/- 0.59	5.5 +/- 0.57	8.1 +/- 0.44	53.2	54.5	39.6
3		12.5	4.7 +/- 0.95	8.9 +/- 0.90	8.7 +/- 1.12	40.5	26.4	35.1
4		25.0	4.3 +/- 0.59	8.3 +/- 0.95	9.8 +/- 0.86	45.6	31.4	26.9
5		50.0	5.0 +/- 0.94	8.4 +/- 0.78	8.4 +/- 0.86	36.7	30.6	37.3
6	d-l Nxtio	6.25	4.1 +/- 0.61	6.2 +/- 0.62	8.7 +/- 0.55	48.1	48.7	35.0
7		12.5	4.9 +/- 0.92	9.3 +/- 1.10	9.4 +/- 1.12	37.9	23.1	29.8
8		25.0	4.6 +/- 0.70	8.9 +/- 1.2	10.2 +/- 0.81	41.7	26.4	23.8
9		50.0	5.6 +/- 0.92	8.7 +/- 0.8	9.8 +/- 0.84	29.1	28.0	26.8

2. Dextran induced oedema in the rat.

This test has been carried out like the preceeding one, except that instead of carrageenan 0.1 ml of a 6% suspension w/v of dextran in the same sterile saline solution where injected.

The measurement of the paw volume (in milliliters) was carried out before the injection and at 0.5, 1 and 2.5 hours after the injection.

The results reported in the table 3 confirm the anti-inflammatory activity of both isomers, with a slight superiority of d-d isom r.

TABLE 3

Effects of oral administration of d-d Nxtio and d-l Nxtio on a dextran-induced oedema in the rat

GROUP	TREATMENT	DOSE mg/Kg p.o.	MEAN INCREASE IN PAW VOLUME			% INHIBITION OF SWELLING		
			0.5	1	2.5	0.5	1	2.5
1	vehicle	-	1.09 +/- 0.05	1.28 +/- 0.04	1.08 +/- 0.06	-	-	-
2	d-d Nxtio	6.25	1.03 +/- 0.04	1.00 +/- 0.03	0.72 +/- 0.04	5.5	21.9	33.3
3		12.5	1.12 +/- 0.08	1.16 +/- 0.04	0.83 +/- 0.06	0	9.4	23.2
4		25.0	1.09 +/- 0.02	1.11 +/- 0.04	0.81 +/- 0.03	0	13.3	25.0
5		50.0	1.24 +/- 0.05	0.90 +/- 0.04	0.73 +/- 0.02	0	29.7	32.4
6	d-l Nxtio	6.25	1.04 +/- 0.08	1.03 +/- 0.07	0.85 +/- 0.07	4.6	19.5	21.3
7		12.5	1.11 +/- 0.04	1.11 +/- 0.08	0.78 +/- 0.08	0	13.3	26.8
8		25.0	1.12 +/- 0.06	1.14 +/- 0.06	0.80 +/- 0.06	0	11.0	26.0
9		50.0	1.20 +/- 0.05	1.10 +/- 0.04	0.9 +/- 0.04	0	14.0	16.6

3. Writhing test in the rat.

Groups of 10 rats (Wistar-Charles River) were dosed orally with either vehicle (0.5% tragacanth) or test compounds (d-d and X d-1 Nxtio) at a costant volume of 10 ml/kg according to the treatment table 1.

Forty-five minutes later each rat received an intraperitoneal injection of 1.0 ml of 1% solution of acetic acid. They were then placed in individual cages and the number of writhes elicited by each rat in the following 25 minute period was recorded.

The results of this test are reported in the table 4, from which it can be observed that both diastereoisomers cause a dose dependent inhibition, with a marked superiority of the isomer d-d of the order of 20%.

TABLE 4

Analgesic activities of orally administered compounds in the writhing test - individual animal data

TREATMENT	ORAL DOSE (mg/Kg)	NUMBER OF WRITHES/25 MIN FOR ANIMAL No.										MEAN WRITHING SCORE (+/- s.e.)
		1	2	3	4	5	6	7	8	9	10	
Vehicle	-	49	54	40	65	43	48	23	65	19	57	46.3 +/- 5.24
d-d Nxtlo	50	4	10	16	4	24	4	8	6	3	1	8.0 +/- 2.36
	25	35	7	16	16	5	36	16	36	23	21	21.1 +/- 3.81
	12.5	42	61	23	25	39	46	38	43	9	7	33.5 +/- 5.74
	6.25	47	59	33	46	71	23	26	25	24	47	40.1 +/- 5.52
d-l Nxtlo	50	7	12	10	8	24	7	11	5	9	0	9.3 +/- 1.95
	25	24	15	32	15	7	28	25	31	20	25	22.2 +/- 2.51
	12.5	56	65	31	37	44	52	35	41	25	10	39.6 +/- 5.03
	6.25	48	51	45	39	31	34	46	37	26	72	42.9 +/- 4.09

4. Randall-Selitto test in the rat

Male Wistar rats (70-90 g) were starved 18 hours prior to the commencement of the experiment but water was available ad libitum.

Each rat received an injection of 0.1 ml of a 20% suspension of Brewer's yeast in distilled water beneath the plantar aponeurosis of the left hind paw.

One hour later the pain thresholds of both the inflamed (yeast injected) and normal hind paw were measured using an analgesiometer designed by U. Basile; the animals were then dosed orally with vehicle (0.5% tragacanth) or test compounds at a constant dose volume of 10 ml/kg.

There were 10 rats in each drug-treated group and 20 rats in the vehicle-treated group.

The pain thresholds of the inflamed and normal hind paws were again measured at 1, 2 and 4 hours after dosing.